MK-3475

BACKGROUND INFORMATION
FOR
THE PEDIATRIC SUBCOMMITTEE OF THE ONCOLOGIC DRUGS ADVISORY COMMITTEE MEETING

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Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
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1 EXECUTIVE SUMMARY

MK-3475 is a potent and highly selective humanized monoclonal antibody of the IgG4/kappa isotype designed to directly block the interaction between programmed cell death (PD)-1 and its ligands, PD-L1 and PD-L2, thereby enhancing tumor regression and ultimately immune rejection.

Merck is currently evaluating or planning to evaluate MK-3475 in various adult oncology indications, including: locally advanced or metastatic melanoma, non-small cell lung cancer (NSCLC), colorectal carcinoma, urothelial tract carcinomas, triple-negative breast cancer, squamous cell carcinoma of the head and neck, gastric cancer and hematologic malignancies. Protocol 001 (PN 001), an open-label Phase I study, is being conducted to evaluate the safety and clinical activity of MK-3475 when administered as monotherapy. The dose escalation portion of this study evaluated three dose levels of single agent MK-3475 (1, 3 and 10 milligram per kilogram) in subjects with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities (DLTs) were observed; therefore, a maximum-tolerated dose has not been determined. The ongoing expansion part of this study is evaluating MK-3475 in subjects with advanced melanoma and NSCLC. Preliminary results from PN001 have been reported, including 135 patients with locally advanced or unresectable melanoma [1] and 38 patients with NSCLC [2]. In both melanoma and NSCLC patients, MK-3475 was generally well tolerated across dose levels with the majority of adverse event findings being reported classified as grade one or two. Sustained anti-cancer activity was observed in both melanoma and NSCLC patients treated with MK-3475.

To date no clinical trials have been undertaken with MK-3475 in subjects under the age of 18 years. However, Merck is committed to evaluating the risks and benefits of MK-3475 treatment in pediatric malignancies.

2 MK-3475 REGULATORY HISTORY

The initial investigational new drug (IND) application for MK-3475 was submitted to the FDA on December 9, 2010. Orphan drug designation for Stage IIB through Stage IV melanoma was granted by FDA on November 20, 2012. Breakthrough Therapy designation was granted for the treatment of unresectable or metastatic melanoma that is refractory to ipilimumab treatment and for the treatment of unresectable or metastatic melanoma in patients who have not received prior ipilimumab therapy by FDA on January 17, 2013. On April 17, 2013 FDA granted MK-3475 a pediatric waiver for advanced melanoma indications based upon the prior orphan drug designation in Stage IIB through Stage IV malignant melanoma.

As part of the MK-3475 global development program, a pediatric investigational plan (PIP) is currently under discussion with EMA.

MK-3475 is not currently approved for any indication in any market at this time.

3 MK-3475 PHARMACOLOGIC RATIONALE

3.1 Drug Substance Structure

MSD's MK-3475 antibody is an IgG4/kappa isotype designed to directly block the interaction between programmed death (PD) -1and its ligands (PD-L1 and PD-L2), without antibody dependent cell-mediated cytotoxicity or complement dependent cytotoxicity. The MK-3475 antibody was generated by humanization of the parental murine anti-human PD-1 antibody.

3.2 3.2 Mechanism of Action

The importance of intact functions of immune surveillance in controlling outgrowth of neoplastic transformations has been known for decades. Accumulating evidence shows a correlation between tumor infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies, irrespective of subsequent treatment. In particular, the presence of CD8+ T cells and the ratio of CD8+ effector T cells / FoxP3+ regulatory T cells correlates with improved prognosis and long-term survival in solid malignancies such as ovarian, colorectal and pancreatic cancer, hepatocellular carcinoma (HCC), melanoma (MEL) and renal cell carcinoma (RCC). TIL can be expanded ex vivo and re-infused, inducing substantial and durable objective tumor responses in cancers such as melanoma [3; 4].

The normal function of PD-1, expressed on the cell surface of activated T cells under healthy conditions is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4, which has been shown to negatively regulate T-cell receptor

signaling upon engagement of its ligands (PD L1 and/or PD-L2). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70, which are involved in the CD3 T-cell signaling cascade [5; 6; 7; 8]. PD-1 blockade enhances functional activity of the target lymphocytes to facilitate tumor regression and ultimately immune rejection. The PD-L1 (one of the ligands for PD-1) expression level on tumor cells has been found to generally correlate with prognosis and survival in various cancers.

Based on the correlation of clinical prognosis with PD-L1 expression among multiple cancers, it is highly suggested that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered a target for therapeutic intervention. Therapeutic studies in mouse models show that administration of antibodies blocking PD-1/PD-L1 interaction enhances infiltration of tumor-specific CD8+ T cells and leads ultimately to tumor rejection, either as a monotherapy or in combination with other treatment modalities. Blockade of the PD-1 pathway effectively promoted CD8+ T cell infiltration into the tumor and the presence of IFN-γ, granzyme B and perforin, indicating that the mechanism of action involved local infiltration and activation of effector T cell function in vivo [9; 10; 11; 12; 13; 14].

4 MK-3475 NONCLINICAL DATA

4.1 Toxicology Studies

A comprehensive nonclinical toxicity program has been conducted with MK-3475.

The safety of MK-3475 was characterized in a 1-month and in a 6-month repeat-dose toxicity study in Cynomolgus monkeys when administered as IV doses of MK-3475 every other week for a total of 12 doses. MK-3475 was well-tolerated. In both studies, no findings of toxicological significance were observed and the NOAEL was ≥ 200 mg/kg.

While the nonclinical development program does not contain specific toxicology studies conducted in juvenile animals, the 6-month monkey study was initiated with monkeys approximately 1 to 3 years of age at study initiation. This correlates to a human age approximately equivalent to late toddler to young adolescent using an age conversion factor of 4, which takes into account the differences in physiological development[15]. The NOAEL of 200 mg/kg in Cynomolgus monkeys, the highest dose tested in the 6-month study, corresponds to a 15-fold exposure multiple compared to the human clinical dose of 10 mg/kg. Therefore, the 6-month chronic toxicity study in Cynomolgus monkeys provided general assessment of potential effects of MK-3475 on growth and development in young population.

There were no findings of toxicological significance in any of the parameters examined, including clinical observations, organ weights, hematology, serum chemistry, gross and microscopic observations. In addition, based on weight of evidence approach, as recommended in the guideline for Immunotoxicity Studies for Human Pharmaceuticals (ICH

S8 Guidance), there were no effects on the immune system in that study. The assessment of hematology, organ weight, and macroscopic and histopathologic evaluation of the spleen, thymus, lymph nodes, bone marrow, Peyer's patches and BALT did not detect any effects of MK-3475 on the immune system in young non-human primates. Results show no evidence of immune related or inflammatory adverse effects, or any adverse effects on lymphoid tissues.

Since the 6-month repeat-dose toxicity study of MK-3475 conducted using monkeys 1 to 3 years of age at study initiation did not show any cause for concern for immune-mediated disorders and the immune system is developed in non-human primates prenatally[16], it is unlikely that a routine juvenile toxicology study of 3-month duration in younger monkeys (after weaning at 4-6 months old to 1-year-old) would be more sensitive than the model described above to identify additional risks in children.

Therefore, based upon the nonclinical and clinical safety data for MK-3475, Merck proposes that no studies in juvenile non-human primates are needed to support treatment of pediatric populations with advanced cancer in accordance to ICH S9.

There are no plans for any additional preclinical studies to support this program.

5 CLINICAL DEVELOPMENT OF MK-3475 IN ADULTS

Currently ongoing studies in adult melanoma only enroll subjects above 18 years of age. There are three ongoing clinical trials evaluating MK-3475 as monotherapy in advanced or metastatic melanoma either refractory to prior treatment or in newly diagnosed patients.

Table 1 outlines this current program with MK-3475.

Table 1 Ongoing MK-3475 Clinical Trials in Adults

Study identifier	Type of study/design features	Study population	Primary endpoint(s)
PN 001 (On-going)	Open label Phase I Study of IV MK-3475	Progressive locally advanced or metastatic carcinoma especially melanoma and non-small cell lung carcinoma	ORR and DCR
PN 002 (On-going)	Randomized, Phase II Study for IV MK-3475 versus chemotherapy	Approximately 510 patients with advanced melanoma refractory to ipilmumab in patients ≥18 years of age	Progression-free survival (PFS) and overall survival (OS)
PN 006 (On-going)	Multicenter, randomized, controlled, three arm Phase III study of 2 doses of IV MK-3475 versus Ipilumamab (IPI)	Approximately 645 patients with diagnosed unresectable or metastatic MEL that have not received treatment with ipilumumab	Progression Free Survival (PFS) and overall survival (OS)

Study identifier	Type of study/design features	Study population	Primary endpoint(s)
PN 010 (On-going)	Multicenter, randomized, open-label Phase II/III study of 2 doses of IV MK-3475 versus Docetaxel	Approximately 920 patients diagnosed with NSCLC who have progressed after platinum-containing therapy	Progression Free Survival (PFS) and Overall Survival (OS)
PN 011 (On-going)	Non-randomized, Phase I, open-label two-part study of I V MK-3475 monotherapy and MK-3475 combination therapy with a platinum-containing regimen	Approximately 30 patients in successive cohorts with advanced solid tumors and NSCLC	Number of participants experiencing dose limiting toxicities (DLTs)
PN 012 (On-going)	Multicenter, non-randomized, Phase I, open-label study of MK-3475	Approximately 114 patients with urothelial tract carcinomas, triple-negative breast cancer, squamous cell carcinoma of the head and neck and gastric cancer	Number of participants experiencing dose limiting toxicities (DLTs)
PN 013 (On-going)	Multcenter, non-randomized Phase I, open-label study of MK-3475	Approximately 100 patients in multiple cohorts with hematologic disease	Overall response rate (ORR), complete remission rate (CRR) and/or number of participants experiencing adverse events

Study identifier	Type of study/design features	Study population	Primary endpoint(s)
PN 016 (On-going)	Non-randomized, Phase II, open-label study of MK-3475	Approximately 71 patients with microsatellite unstable (MSI) positive or negative colorectal and other tumors	Progression Free Survival (PFS)

5.1 Preliminary Findings from the PN 001 Study

PN 001 is a Phase I, open-label, clinical trial to evaluate the safety, tolerability and maximum administered dose as well as obtain preliminary anti-tumor activity in advanced solid tumors with cohort expansions in melanoma and NSCLC. Preliminary safety, pharmacokinetic and tumor response data from melanoma and NSCLC patients treated in the PN 001 study have recently been published [17].

Pharmacokinetics (PK)

Serum MK-3475 samples were obtained before and after drug administration. MK-3475 serum concentrations were lower by a factor of approximately 5 in patients receiving 2 vs. 10 mg per kilogram every 3 weeks. Steady state trough concentrations were 20% greater in patients receiving 10 mg per kilogram every 2 weeks vs. those receiving the same dose on an every 3 week schedule. The increase in trough serum concentrations over time is consistent with the half-life of MK-3475 of about 2 to 3 weeks [18].

Melanoma [1]

A total of 135 patients with advanced melanoma were treated. Of those treated, 117 had radiographically measurable disease confirmed by independent radiologic review. Initially, patients were enrolled in a cohort that received MK-3475 at a dose of 10 mg per kilogram every 2 weeks. Subsequently, additional patients were enrolled in concurrent cohorts that received MK-3475 at 10 mg per kilogram or 2 mg per kilogram every 3 weeks. Distinction was made between patients who had received prior treatment with ipilimumab (48 patients) and those who had not (87 patients) to provide preliminary safety and anti-tumor data on the basis of prior or no prior ipilimumab treatment. The majority of patients (38 of 48) had

received three or more ipilimumab infusions. More than 50% of all patients enrolled had visceral metastases (stage M1c), 25% had an elevated lactate dehydrogenase level and approximately 9% has a history of brain metastases.

The confirmed response rate across all dose cohorts, also evaluated by central radiologic review according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, was 38% (95% confidence interval [CI], 25 to 44), with the highest confirmed response rate observed in the cohort that received 10 mg per kilogram every 2 weeks (52%; 95% CI, 38 to 66). The response rate did not differ significantly between patients who had or had not received prior ipilimumab treatment (confirmed response rate, 38% [95% CI, 23 to 55] and 37% [95% CI, 26 to 49], respectively). Responses were durable, with a median duration of response not reached with a median follow-up time of 11 months). 81% of the patients who had a response (42 of 52) were still receiving treatment at the time of analysis in March 2013. The overall median progression-free survival among the 135 patients was longer than 7 months. The estimated median for overall survival was not reached. See Table 2.

Table 2 Objective Response Rates

Table 4 Objective Response Rate, According to Dosing Regimen and Status with Respect to Prior Therapy with Ipilimumab as Assessed According to Two Criteria*

Regimen and Ipilimumab Status	RECIST				Immune-Related Response	
	No. of Patients	Confirmed and Unconfirmed Objective Response	Confirmed Objective Response	Duration of Response†	No. of Patients	Confirmed Objective Response
		no. (% [95% CI])		*mo*		*no. (% [95% CI])*
10 mg/kg every 2 wk						
No prior ipilimumab	39	21 (54 [37–70])	19 (49 [32–65])‡	1.9–10.8	41	23 (56 [40–72])
Prior ipilimumab	13	8 (62 [32–86])	8 (62 [32–86])§	2.8–8.3	16	9 (56 [30–80])
Total	52	29 (56 [41–69])	27 (52 [38–66])	1.9–10.8	57	32 (56 [42–69])
10 mg/kg every 3 wk						
No prior ipilimumab	19	7 (37 [16–62])	5 (26 [9–51])	2.6–5.6	24	8 (33 [16–55])
Prior ipilimumab	26	9 (35 [17–56])	7 (27 [12–48])	2.8–8.3	32	7 (22 [9–40])
Total	45	16 (36 [22–51])	12 (27 [15–42])	2.6–8.3	56	15 (27 [16–40])
2 mg/kg every 3 wk, no prior ipilimumab	20	7 (35 [15–59])	5 (25 [9–49])¶	2.1–5.5	22	3 (14 [3–35])
Total‖	117	52 (44 [35–54])**	44 (38 [25–44])	1.9–10.8	135	50 (37 [29–45])

* The efficacy population of patients with measurable disease was assessed by means of an independent, central, blinded radiologic review with the use of the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, and by means of investigator assessment with the use of immune-related response criteria. The latter was the primary end point of the study. Responses based on immune-related response criteria included only those that were confirmed on two consecutive scans obtained at least 28 days apart.

† The duration of response was defined as the time from the first response to the time of documented progression or, in the case of censored data, the most recent tumor assessment. All the lower and upper ranges listed here are for censored data and refer to the time from the first response to the most recent tumor assessment, except for the lower range in the group with no prior ipilimumab, as well as the total cohort, receiving 10 mg per kilogram of body weight every 3 weeks; these two lower ranges refer to the time from first response to the time of documented progression. Only confirmed responses were included in the calculation of duration of response.

‡ Three of these patients had a complete response.

§ Two of these patients had a complete response.

¶ One of these patients had a complete response.

‖ The confirmed response rate, according to RECIST, version 1.1, was 38% (95% CI, 23 to 55) among patients who had received prior ipilimumab treatment and 37% (95% CI, 26 to 49) among patients who had not received prior ipilimumab treatment.

** Six patients with initial responses were awaiting confirmation of the response at the time of the data cutoff for this report. One response has since been confirmed, but since it was confirmed after the data cutoff for the current analysis, the data on overall response rate have not been modified.

Of the 135 patients who received at least one dose of MK-3475, 79% reported drug-related adverse events of any grade, and 13% reported grade 3 or 4 drug-related adverse events. Generalized symptoms, including fatigue and asthenia, fever and chills, myalgias and headaches, were reported frequently but were of low grade in more than 95% of the reported cases. Treatment-related pneumonitis was reported in 4% of the patients; none of the cases were grade 3 or 4. Rash and pruritis were reported in 21% of the patients; with grade 3 or 4 pruritis only identified in 1% and grade 3 or 4 rash in 2% of patients. The highest incidence of overall treatment- related adverse events was seen among the patients who received 10 mg of MK-3475 per kilogram

every 2 weeks, as compared with the patients receiving 10 mg per kilogram every 3 weeks and those receiving 2 mg per kilogram every 3 weeks (23%, vs. 4% and 9%, respectively).

Non-small Cell Lung Cancer [2]

MK-3475 was administered at 10 mg/kg every three weeks to patients with NSCLC previously treated with two systemic regimens. At least one measurable tumor lesion, ECOG performance status of zero or one, and adequate laboratory function were required for eligibility. A new tumor biopsy no earlier than 60 days before the first dose of MK-3475 was required for study entry. Imaging assessments per investigators were performed every nine weeks until confirmed disease progression utilizing the immune-related response criteria (irRC). Independent central review of images was assessed with RECIST v1.1. PD-L1 expression on the pretreatment tumor sample was determined by immunohistochemistry.

Between April 2012 and September 2012, thirty-eight patients were enrolled. The median age was 63 years (range, 34-85 years), with 42% men and 42% with an ECOG performance status of zero. Previously treated, stable brain metastases were allowed and were present in 10%. Seven patients had an EGFR mutation, eight patients had a KRAS mutation, and one patient had an ALK gene rearrangement in their tumor. Fifty percent of patients experienced drug-related adverse events; the most common were fatigue, rash, and pruritus (16% each). The incidence of diarrhea was 13% (only grade 1 or 2 reported). One case of a drug-related grade 3-4 adverse event (grade 3 pulmonary edema: 3%) was seen. There were no drug-related fatalities. Using investigator-assessed irRC, the objective response rate (ORR; confirmed and unconfirmed) was 24%, including squamous and nonsquamous subtypes. Similar results were obtained using RECIST v1.1, yielding an ORR (confirmed and unconfirmed) of 21%. Most responses by irRC were observed by the time of first planned assessment at Week 9. The median duration of response by irRC has not been reached, with a median duration of follow-up of 9 months (minimum, 6 months). As of June 2013, seven of the nine responding patients by irRC continue on therapy. Pretreatment tumor PD-L1 expression was a statistically significant predictor of response. In patients with evaluable tumor PD-L1 expression, all confirmed responses by RECIST v1.1 (and irRC) occurred in patients with tumors strongly positive for PD-L1 expression.

6 PROPOSED MK-3475 DEVELOPMENT IN PEDIATRIC PATIENTS

Of the cancer indications for which α-PD-1 therapy has demonstrated clinically relevant anti-cancer activity, melanoma is the only solid tumor type that occurs in children, albeit rarely. Therefore, the pediatric development plan includes melanoma, but also seeks to identify additional pediatric tumors that could be amenable to α-PD-1 therapy. This will be accomplished by:

1. Evaluating genomic databases and banked tumor tissue for evidence of PD-1 pathway activation in pediatric cancers

2. Evaluating preliminary efficacy in a pediatric Phase I safety, PK, and dose-finding study
3. Using an adaptive Phase II design to explore multiple indications for efficacy signals, expanding single cohorts in which clinical activity is observed. Enrollment at this stage will be based on demonstrating intra-tumor PD-L1 expression by immunohistochemistry (IHC) in order to increase the chance of response to MK-3475.

At the conclusion of Phase II study in pediatric patients, responses in each enrolled solid tumor will be evaluated in order to select one indication for which a randomized Phase II/III safety and efficacy study could be conducted to generate additional support for pediatric use.

6.1 Patient Enrichment Biomarker Strategy

PD-L1 expression on tumor cells measured by IHC is the most advanced predictive biomarker for response to an α-PD-1 therapy. Merck has developed an IHC assay, which is based on a mouse monoclonal antibody (clone 22C3), capable of detecting PD-L1 in formalin-fixed paraffin-embedded (FFPE) human tumor samples. Preliminary data from MK-3475 clinical trials support its further investigation as a predictive biomarker. If PD-L1 protein expression is predictive of response to MK-3475, selection of patients according to tumor PD-L1 expression level may help avoid treating many patients who might not benefit from the drug. Table 3 describes the current plans for application of tumor PD-L1 IHC testing in pediatric development.

Table 3 ICH Testing Approach

Trial Stage	Application
Phase I Dose Escalation Study	Retrospective
Phase II Adaptive Indication Finding Study	Prospective Patient Enrichment
Phase III Safety and Efficacy Study	Pending emerging data from Phase I and II, could be used prospectively (enrichment or stratification)

6.2 Pediatric Dosing Rationale

It is not expected that developmental differences between adults and children will affect the PK or PD of monoclonal IgG4 antibodies such as MK-3475. As in adults, dosing will be based on body weight. Safety, PK and PD of at least two doses will be evaluated in order to define the pediatric recommended phase 2 dose (RP2D). Dose Level 1 will target the equivalent of 50% exposure at the adult maximum administered dose (MAD). PK results

from ongoing PN 001 study will determine the final dose levels and schedule to be evaluated. The RP2D will be based on a safe and tolerated dose that best approximates AUCss of the adult RP2D. The RP2D will also be a safe and tolerated dose for which concentrations exceed those associated with saturation of an α-PD-1 pharmacodynamic biomarker (IL-2 release assay) based on adults treated with MK-3475.

6.3 Pediatric Formulation Development

A separate pediatric formulation will not be developed, as the available IV formulation will support dosing in the pediatric population across ages.

6.4 6.4 Proposed Study Approach

Two studies are planned. The first study will be a multi-center, open label, single arm, seamless Phase I and Phase II trial of intravenous MK-3475 in pediatric patients from 6 months to <18 years of age with advanced melanoma and advanced, relapsed or refractory solid tumors or lymphoma. The objectives of Part 1 of the study are to characterize the safety, PK and preliminary efficacy in children with advanced melanoma or advanced relapsed/refractory solid tumors and lymphoma, and to establish the pediatric RP2D dose for further safety and efficacy evaluation in Part 2 of the proposed study. Accordingly, the primary endpoints relate to safety and PK. Tumor biopsies will be collected and evaluated retrospectively. The objectives for Part 2 are to further evaluate safety and efficacy at the pediatric RP2D in children with advanced melanoma or advanced relapsed/refractory solid tumors and lymphoma. Accordingly, the primary endpoints of Part 2 relate to safety and objective tumor response rates. Prioritization of tumors to be included in Part 2/Phase II of the first study will be informed by both the non-clinical evaluation (genomic databases and banked tumor tissue for evidence of PD-1 pathway activation in pediatric cancers) and clinical signals from Part 1. Additionally, an adaptive design will be used in Part 2 of the study to increase the sample size in cancers for which ongoing results indicate anti-tumor activity of MK-3475. It is expected that a minimum of 50 patients will be initially enrolled in up to 10 different pediatric cancer types at the RP2D. Following an interim analysis of RECIST1.1 objective response rates (ORR) with a minimum of 5 patients enrolled in each tumor type, additional patients may be enrolled in a specific tumor type (up to 20-25 patients total). Tumors for which there is a strong non-clinical rationale, or for which clinical signals have been observed in Part 1, could be emphasized in Part 2 without taking a staged approach, i.e. enroll all 20-25 patients without an interim assessment. In order to select pediatric patients who have an increased chance of benefiting from MK-3475 therapy, patients will be enrolled on the basis of positive tumor PD-L1 expression by IHC in Part 2.

At the conclusion of Part 2, responses in each studied solid tumor type will be evaluated, and the 95% CI will be computed for the ORR within each solid tumor type based on the exact binomial distribution. If more than one indication are similarly promising, then the

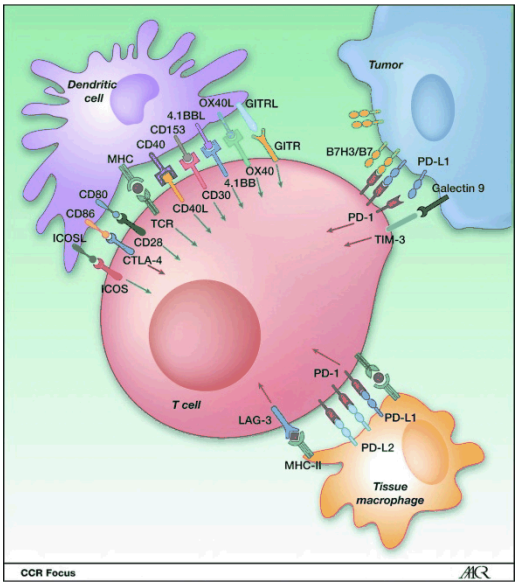
indication with the greatest unmet medical need will be studied in the subsequent Phase II/III trial.

The second study will be a randomized Phase II/III safety and efficacy study in a solid tumor type selected based on the conclusion of Part 2 of the proposed Phase I/II study. Details of this Phase II/III study design will depend on the pediatric indication selected, e.g. eligibility, comparator, primary endpoint. The primary objective for the study will be to evaluate a survival endpoint appropriate for the selected indication (progression-free survival and or overall survival) in patients receiving MK-3475 monotherapy relative to the comparator. Secondary objectives will be to compare the clinical activity of MK-3475 monotherapy versus the comparator in pediatric subjects with the selected indication as measured by ORR, Duration of Response, Disease Control Rate and to assess the safety and tolerability of MK-3475 monotherapy versus the comparator.

6.5 Challenges to Pediatric Development of MK-3475

A key challenge in developing MK-3475 in pediatrics is to identify tumor types most likely to respond to α-PD-1 therapy. A central hypothesis is that tumors commonly have a "stalled" anti-tumor cytotoxic T cell (CTL) immune response, which may be re-activated through PD-1 blockage with MK-3475. Figure 1 [19] illustrates the role of the PD-1 pathway in abrogating tumor specific T cell responses. MK-3475 blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L1, which can result if reactivation of tumor specific T cells.

Figure 1 PD-1 Pathway



Data from NSCLC patients treated with MK-3475 as well as results from clinical studies of other PD-1 or PD-L1 antibodies indicates that PD-L1 expression by IHC correlates with clinical outcome. Banked pediatric FFPE tumor tissues will be evaluated for evidence of PD-1 pathway up-regulation in order to prioritize specific cancer types for phase I and II development. Using an adaptive Phase II design, multiple indications will be evaluated for efficacy signals, with expansion of single cohorts in which clinical activity is observed. Further development would be in the most promising indication identified from the Phase II study.

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